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(54) **Method of producing formamide compounds.**

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Description

The present invention relates to a method of producing formamide compounds and, more particularly, to a method of producing formamide compounds by formylating amines via transamidation.

Formylated compounds of amines, i.e., formamides are very important materials as solvents, drugs, pesticides as well as intermediates for preparing such solvents, drugs, and pesticides in chemical industries. In order to derive nicotine from nornicotine, it is preferable to produce nicotine via N'-formylnornicotine as an intermediate rather than direct methylation of nornicotine.

Two methods are known for formylating amines. One method involves reaction of an amine with carbon monoxide under heating and high pressure. Another method involves reaction of an amine with separately prepared phenyl formate. However, these methods require relatively complicated reaction procedures and expensive apparatuses.

Another method is also known for producing formamide compounds by formylating amines via transamidation. This method consists of reacting dimethylformamide with an amine under the formylation conditions of the amine. This method has advantages in that dimethylformamide is commerically available at low cost, formylation can be easily performed, and a special apparatus is not needed. In the transamidation reaction, the following equilibrium reaction is established:

$(CH_3)_2NCHO + R^1R^2NH \rightleftarrows (CH_3)_2NH + R^1R^2NCHO$ in this reaction, the reactants can be transferred to the products without using a catalyst, by heating to a high temperature to remove the dimethylamine.

(Synthesis, 1973, P. 361). This formylation method can indeed produce a desired formamide compound with a high yield, but a long reaction time is required.

In the above literature, an acid catalyst such as sulfuric acid is used in the formylation reaction. When the acid catalyst is used, the reaction time can be shortened to some extent, but other problems such as corrosion of a reaction chamber occur. In addition, since the acid catalyst is a homogeneous catalyst, the reaction product must be washed to remove the acid catalyst after the reaction, and a problem of posttreatments, e.g., a waste fluid disposition, occurs.

As described above, in the conventional method of producing formamide compounds on the basis of the reaction of dimethylformamide and amines, the long reaction time is required if the catalyst is not used.

If the acid catalyst is used, the reaction chamber is corroded, and post-treatments are required.

It is, therefore, an object of the present invention to provide a method of producing formamide on the basis of formylation of amines with dimethylformamide, wherein the reaction can be completed within a relatively short period of time and the post-treatment after the reaction can be easily performed.

According to the present invention, there is provided a method of producing a formamide compound which comprises reacting dimethylformamide and an amine in the presence of a solid catalyst consisting of at least one metal oxide selected from the group consisting of oxides of metals of Groups III, IV, and V of the Periodic Table.

According to the present invention, in formylation of an amine with dimethylformamide, a catalyst is used which consists of at least one metal oxide selected from the group consisting of oxides of metals of Groups III, IV, and V of the Periodic Table. Examples of the catalyst include silica gel, titania, zirconia, alumina, silica alumina, and natural or synthetic zeolite. These catalysts are commercially available at low cost and can be used in the form of granules or powders.

The present inventors have made studies on catalysts used in a reaction between dimethylformamide and an amine compound to find that the solid catalyst of the above-mentioned metal oxide can sufficiently accelerate the formylation reaction of the amine and can be easily separated and recovered after reaction because this catalyst is a heterogeneous catalyst.

Since the reaction to which the above-mentioned solid catalyst is applied is a known reaction between dimethylformamide and the amine, an amine used as a material for the formylation reaction may be a primary amine or a secondary amine (excluding dimethylamine) including an aliphatic amine, an alicyclic amine, an aromatic amine, and a heterocyclic amine. Examples of such an amine are an alkylamine (e.g., ethylamine, propylamine, isopropylamine, butylamine, decylamine, benzylamine, or α-methylbenzylamine), dialkylamine, a cycloalkylamine (e.g., cycloalkylamine having 3 to 8 carbon atoms), dicycloalkylamine, an aromatic amine (e.g., phenylamine or naphthylamine), and a heterocyclic amine (e.g., piperidine, pyrrolidine, or nornicotine).

The formylation reaction of the amine with dimethylformamide can be performed by bringing the amine into contact with dimethylformamide in the presence of the catalyst of the present invention under the formylation conditions for the amine. This reaction can be performed in the gaseous or liquid phase. In addition, the reaction is relatively simple and safe and can be performed regardless of the scale of reaction system.

In order to perform the formylation reaction in the liquid phase, the above-mentioned catalyst is added to a dimethylformamide solution (i.e., an excessive amount of dimethylformamide is present) containing the amine, and the resultant solution is heated. The catalyst can be used in an amount of 0.01 to 10 g, preferably 0.5 to 3 g, per millimole of the amine. The reaction is generally carried out at a temperature of 100°C to 180°C and is usually performed under reflux. In this reaction, an appropriate inert diluting solvent may be added to dilute the reaction mixture. After the reaction, the catalyst is removed by filtering,

and the filtered reaction mixture is subjected to fractional distillation to isolate the formamide compound formed. In this case, if the produced formamide compound has a boiling point sufficiently higher than that of dimethylformamide, dimethylformamide is simply evaporated to obtain a formamide compound having a sufficiently high purity. The catalyst recovered by filtration can be repeatedly used in the formylation reaction.

In order to perform the formylation reaction in the gaseous phase, the catalyst is filled in a reaction tube and is heated to a predetermined reaction temperature. The dimethylformamide solution of the amine is supplied to the filled catalyst layer directly or by using a proper inert carrier gas. The outlet of the reaction tube is cooled by a coolant such as water or ice to condense the produced formamide compound and the nonreacted material. The produced formamide compound can be separated from the condensate following the same procedures as in the liquid-phase reaction described above.

The present invention will be described in detail by way of its examples.

Example 1

0.5 g of a silica gel powder catalyst (100 mesh, available from Marinecrot Corp.) 2 millimole of piperdine and 20 millimole of dimethylformamide were charged in a 50-mℓ round bottom flask, and the resultant mixture was heated and refluxed moderately. Small portions of the reacted solution were sampled after 2 and 5 hours of refluxing to measure yields of the desirsed product, N-formylpiperidine, by using a gas chromatograph. The yields were 67% and 100% after 2 and 5 hours, respectively.

The same procedures as described above were performed except that active alumina C-1A (tradename) available from Mizusawa Kagaku Kogyo K.K., titania (anatase) available from Wako Junyaku Kogyo KK, silica alumina (the grain size: 24 to 60 meshes after pulverization) available from Mizusawa Kagaku Kogyo K.K., zirconia (grain size: 24 to 60 meshes after pulverization of pellets) available from Daiichi Kigenso Kagaku Kogyo K.K., and zeolite A-3 (tradename) (grain size: 24 to 60 meshes after pulverization of balls) available from Toyo Soda Kogyo K.K. were used in place of silica gel. Results are shown in Table 1 below, which includes the results of using silica gel.

Table 1

Catalyst	Yield of N-Formylpiperidine	
	After 2 hours (%)	After 5 hours (%)
Silica Gel	67	100
Alumina	56	100
Titania	52	100
Silica Alumina	61	100
Zirconia	1	3
Zeolite	11	28

When zirconia and zeolite were used, the yields were lower than those for other catalysts. However, it is seen that these catalysts accelerate the N-formylpiperidine-producing reaction by formylation after short period of time, which was difficult in the conventional methods.

Example 2

2 g of zirconia particles as in Example 1 were filled in a glass tube having an inner diameter of 6.5 mm and an outer diameter of 8.5 mm. The glass tube was placed in an electric furnace. This reaction system was heated to 250°C, and a solution of 10 millimole of cyclohexylamine in 50 mℓ of dimethylformamide was supplied at a rate of 5 mℓ/min by a microfeeder while nitrogen gas was supplied at a rate of 60 mℓ/min to the glass tube. The material passing through the catalyst layer filled in the glass tube was cooled and condensed at the outlet of the glass tube.

The resultant reaction mixture was subjected to quantative measurement of the desired product, N-formylcyclohexylamine, by using a gas chromatograph. The yield was 85%, and the remaining component was cyclohexylamine.

Example 3

0.5 g of silica gel as in Example 1, 2 millimole of α-methylbenzylamine and 20 millimole of dimethylforma-

mide were charged in a 50-mℓ round bottom flask. The resultant reaction mixture was heated and refluxed. A portion of the reaction mixture was sampled after two hours of refluxing and was analyzed using a gas chromatograph. α-methylbenzylamine as a starting material was not detected, and N-formyl-α-methylbenzylamine was found to be produced at a yield of 89%.

The same procedures as described above were followed, except that dicyclohexylamine, cyclohexylamine, decylamine, or pyrrolidine was used in place of α-methylbenzylamine. Results are shown in Table 2 below, in which results of using α-methylbenzylamine are also listed.

Table 2

Amine	Product	Reaction Time (hours)	Yield (%)
α-methylbenzylamine	N-formyl-α-methylbenzylamine	2	89
Dicyclohexylamine	N-formyldicyclohexylamine	5	66
Cyclohexylamine	N-formylcyclohexylamine	3	93
Decylamine	N-formyldecylamine	5	84
Pyrrolidine	N-formylpyrrolidine	3	100

Example 4

1.48 g of racemic-nornicotine were dissolved in 30 mℓ of dimethylformamide, and 1 g of titania as in Example 1 was added. The resultant mixture was heated and refluxed moderately for 5 hours. The mixture was then cooled to room temperature and the titania was removed from the reaction mixture by filtering. The filtrate was concentrated by removing dimethylformamide under reduced pressure. The desired product, N'-formylnornicotine, was gradually precipitated during concentration. By completely removing dimethylformamide, 1.55 g (yield: 88.1 %) of N'-formylnornicotine were obtained.

According to the present invention as described above, the formamide compound can be produced within a relatively short period of reaction time. In addition, the catalyst can be easily recovered after the reaction, and the separation of the product can also be easily performed.

Claims

1. A method of producing a formamide compound, which comprises reaction of dimethylformamide and an amine in the presence of a solid catalyst consisting of at least one metal oxide selected from the group consisting of oxides of metals of Groups III, IV, and V of the Periodic Table, thereby producing a formamide compound corresponding to the amine.

2. The method according to claim 1, wherein said solid catalyst is selected from the group consisting of silica gel, titania, zirconia, alumina, silica alumina, and zeolite.

3. The method according to claim 1 or 2, wherein said amine is a primary or secondary amine.

4. The method according to any of claims 1 to 3, wherein said amine is an aliphatic amine, an alicyclic amine, an aromatic amine, or a heterocyclic amine.

5. The method according to any of claims 1 to 4, wherein said amine is ethylamine, propylamine, isopropylamine, butylamine, decylamine, benzylamine, α-methylbenzylamine, cyclohexylamine, dicyclohexylamine, phenylamine, naphthylamine, piperidine, pyrrolidine, or nornicotine.

6. The method according to any of claims 1 to 5, wherein said reaction is performed in gaseous phase.

7. The method according to any of claims 1 to 5, wherein said reaction is performed in liquid phase.

8. A method of producing a formamide compound, comprising:
preparing a mixture of a dimethylformamide solution containing an amine, and a solid catalyst consisting

of at least one metal oxide selected from the group consisting of oxides of metals of Groups III, IV, and V of the Periodic Table;
placing the mixture under formylation conditions for the amine with dimethylformamide to produce a formamide compound corresponding to the amine;
filtering the mixture to remove the solid catalyst; and
separating the produced formamide compound from the filtered mixture.

9. The method according to claim 8, wherein said formylation conditions include heating of the mixture under refluxing.

10. The method according to claim 8 or 9, wherein said heating is performed at a temperature of 100°C to 180°C.

11. The method according to any of claims 8 to 10, wherein said solid catalyst is used in an amount of 0.01 to 10g per millimole of said amine.

12. The method according to any of claims 8 to 11, wherein said solid catalyst is used in an amount of 0.5 to 3g per millimole of said amine.

13. The method according to any of claims 8 to 12, wherein said solid catalyst comprises silica gel, titania, zirconia, alumina, or silica alumina.

14. A method of producing a formamide compound, comprising:
heating a mixture of an amine and dimethylformamide to a temperature sufficient to vaporize the mixture;
bringing the vaporized mixture into contact with a solid catalyst bed consisting of at least one metal oxide selected from the group consisting of oxides of metals of Groups III, IV, and V of the Periodic Table to react the amine with the dimethylformamide, thereby producing a corresponding formamide compound;
cooling and condensing the gaseous mixture containing the produced formamide compound; and
separating the produced formamide compound from the condensate.

15. The method according to claim 14, wherein said vaporized mixture is carried by an inert carrier gas.

16. The method according to claim 14 or 15, wherein said solid catalyst bed comprises silica gel, titania, zirconia, alumina, or silica alumina.

Revendications

1. Procédé de préparation d'un composé de formamide, consistant à faire réagir un diméthylformamide et une amine en la présence d'un catalyseur solide constitué d'au moins un oxyde métallique choisi dans le groupe comprenant des oxydes de métaux des groupes III, IV, et V du Tableau Periodique, obtenant ainsi un composé de formamide correspondant à l'amine.

2. Procédé selon la revendication 1, dans lequel ce catalyseur solide est choisi dans le groupe comprenant un gel de silice, le dioxyde de titane, la zircone, l'alumine, un mélange de silice et d'alumine et la zéolite.

3. Procédé selon l'une des revendications 1 ou 2, dans lequel l'amine est une amine primaire ou secondaire.

4. Procédé selon l'une des revendications 1 à 3, dans lequel l'amine est une amine aliphatique, une amine alicyclique, une amine aromatique ou une amine hétérocyclique.

5. Procédé selon l'une des revendications 1 à 4, dans lequel l'amine est l'une des suivantes: éthylamine, propylamine, isopropylamine, butylamine, décylamine, benzylamine, α-méthylbenzylamine, cyclohexylamine, dicyclohexylamine, phénylamine, naphthylamine, pipéridine, pyrrolidine ou nornicotine.

6. Procédé selon l'une des revendications 1 à 5, dans lequel la réaction s'effectue en phase gazeuse.

7. Procédé selon l'une des revendications 1 à 5, dans lequel la réaction s'effectue en phase liquide.

8. Procédé de préparation d'un composé de formamide, consistant à:
préparer un mélange d'une solution de diméthylformamide contenant une amine et d'un catalyseur solide constitué d'au moins un oxyde métallique choisi dans le groupe comprenant des oxydes de métaux des groupes III, IV et V du Tableau Périodique;
placer le mélange dans des conditions de formylation pour l'amine avec le diméthylformamide pour obtenir un composé de formamide correspondant à l'amine;
filtrer le mélange pour retirer le catalyseur solide; et
séparer le composé de formamide obtenu du mélange filtré.

9. Procédé selon la revendication 8, dans lequel les conditions de formylation impliquent de chauffer le mélange à reflux.

10. Procédé selon l'une des revendications 8 ou 9, dans lequel le chauffage s'effectue à une température comprise entre 100°C et 180°C.

11. Procédé selon l'une des revendications 8 à 10, dans lequel la quantité de catalyseur solide utilisée est comprise entre 0,01 et 10g par millimole de l'amine.

12. Procédé selon l'une des revendications 8 à 11, dans lequel la quantité de catalyseur solide utilisée est comprise entre 0,5 et 3g par millimole de l'amine.

13. Procédé selon l'une des revendications 8 à 12, dans lequel le catalyseur solide est choisi dans le groupe comprenant un gel de silice, le dioxyde de titane, la zircone, l'alumine, ou un mélange de silice et d'alumine.

14. Procédé de préparation d'un composé de formamide, consistant à:
chauffer un mélange d'une amine et de diméthylformamide à une température suffisante pour vaporiser le mélange;
amener le mélange vaporisé en contact avec un lit de catalyseur solide constitué d'au moins un oxyde métallique choisi dans le groupe comprenant des oxydes de métaux des groupes III, IV et V du Tableau Périodique pour faire réagir l'amine avec le diméthylformamide, obtenant ainsi un composé de formamide correspondant;
refroidir et condenser le mélange gazeux contenant le composé de formamide ainsi obtenu; et
séparer du condensat le composé de formamide obtenu.

15. Procédé selon la revendication 14, dans lequel le mélange gazeux est transporté par un véhicule gazeux inerte.

16. Procédé selon l'une des revendications 14 ou 15, dans lequel le lit de catalyseur solide comprend un gel de silice, du dioxyde de titane, de la zircone, de l'alumine ou un mélange de silice et d'alumine.

Patentansprüche

1. Verfahren zur Herstellung einer Formamidverbindung, umfassend die Umsetzung von Dimethylformamid mit einem Amin in Gegenwart eines festen Katalysators, bestehend aus mindestens einem Metalloxid, ausgewählt aus der Gruppe, die aus Oxiden von Metallen der Gruppen III, IV und V des Periodensystems besteht, so daß eine dem Amin entsprechende Formamidverbindung erzeugt wird.

2. Verfahren nach Anspruch 1, wobei der feste Katalysator aus der Gruppe Silicagel, Titandioxid, Zirkondioxid, Aluminiumoxid, Siliciumdioxid-Aluminiumoxid und Zeolith ausgewählt ist.

3. Verfahren nach Anspruch 1 oder 2, wobei das Amin ein primäres oder sekundäres Amin ist.

4. Verfahren nach einem der Ansprüche 1 bis 3, wobei das Amin ein aliphatisches Amin, ein alicyclisches Amin, ein aromatisches Amin oder ein heterocyclisches Amin ist.

5. Verfahren nach einem der Ansprüche 1 bis 4, wobei das Amin Ethylamin, Propylamin, Isopropylamin, Butylamin, Decylamin, Benzylamin, α-Methylbenzylamin, Cyclohexylamin, Dicyclohexylamin, Phenylamin, Naphthylamin, Piperidin, Pyrrolidin oder Nornicotin ist.

6. Verfahren nach einem der Ansprüche 1 bis 5, wobei die Umsetzung in der Gasphase ausgeführt wird.

7. Verfahren nach einem der Ansprüche 1 bis 5, wobei die Umsetzung in der flüssigen Phase ausgeführt wird.

8. Verfahren zur Herstellung einer Formamidverbindung, umfassend:
Herstellen eines Gemisches aus einer ein Amin enthaltenden Dimethylformamidlösung und einem festen Katalysator, bestehend aus mindestens einem Metalloxid, ausgewählt aus der Gruppe, die aus Oxiden von Metallen der Gruppen III, IV und V des Periodensystems besteht;
Aussetzen des Gemisches unter Formylierungsbedingungen für das Amin mit Dimethylformamid zur Bildung einer dem Amin entsprechenden Formamidverbindung;
Filtrieren des Gemisches zum Entfernen des festen Katalysators; und
Abtrennen der gebildeten Formamidverbindung von dem filtrierten Gemisch.

9. Verfahren nach Anspruch 9, wobei die Formylierungsbedingungen das Erhitzen des Gemisches während des Rückflußkochens einschließen.

10. Verfahren nach Anspruch 8 oder 9, wobei die Erhitzung bei einer Temperatur von 100°C bis 180°C durchgeführt wird.

11. Verfahren nach einem der Ansprüche 8 bis 10, wobei der feste Katalysator in einer Menge von 0,01 bis 10 g pro Millimol des Amins eingesetzt wird.

12. Verfahren nach einem der Ansprüche 8 bis 11, wobei der feste Katalysator in einer Menge von 0,5 bis 3 g pro Millimol des Amins eingesetzt wird.

13. Verfahren nach einem der Ansprüche 8 bis 12, wobei der feste Katalysator Silicagel, Titandioxid, Zirkondioxid, Aluminiumoxid oder Siliciumdioxid-Aluminiumoxid enthält.

14. Verfahren zur Herstellung einer Formamidverbindung, umfassend:
Erhitzen eines Gemisches aus einem Amin und Dimethylformamid auf eine zum Verdampfen des Gemisches ausreichende Temperatur;
in Kontakt Bringen des verdampften Gemisches zum Umsetzen des Amins mit dem Dimethylformamid mit einem festen Katalysatorbett, bestehend aus mindestens einem Metalloxid, ausgewählt aus der Gruppe, die aus Oxiden von Metallen der Gruppen III, IV und V des Periodensystems besteht, so daß die entsprechende Formamidverbindung gebildet wird;
Abkühlen und Kondensieren des gasförmigen Gemisches, das die gebildete Formamidverbindung enthält; und
Abtrennen der gebildeten Formamidverbindung aus dem Kondensat.

15. Verfahren nach Anspruch 14, wobei das verdampfte Gemisch von einem inerten Trägergas getragen wird.

16. Verfahren nach Anspruch 14 oder 15, wobei das feste Katalysatorbett Silicagel, Titandioxid, Zirkondioxid, Aluminiumoxid oder Siliciumdioxid-Aluminiumoxid enthält.